been amended to properly recite the claims from which they depend. The basis for these amendments is set forth below. Claims 21-28 have been added. Support for the newly added claims resides in the specification at page 12, lines 24-34, and in the Examples at page 19, lines 5-24. No new matter is added by way of claim amendment or the addition of claims.

The Rejections Under 35 U.S.C. §112 Should Be Withdrawn

Claims 1-20 were rejected under 35 U.S.C. §112, first paragraph. The Examiner indicates that the specification, while being enabling for IGF-I and arginine, does not reasonably provide enablement for analogues of IGF-I or arginine. It is alleged that the term "analogues" is too broad and that a skilled artisan would not be able to make and use all of the analogues as claimed. This rejection is respectfully traversed.

Applicants' invention is directed to the combination of IGF-I, or an IGF-I analogue, and a solubilizing agent comprising a guanidinium group, such as arginine and its amino acid analogues, where the combination allows for enhanced solubility of the protein at low temperature and pH of at least about 5.5. Until Applicants' invention, to provide stable IGF-I compositions for refrigerated storage with acceptable IGF-solubility levels, such compositions were maintained at a pH less than about 5.0. Administration of IGF-I at such nonphysiological pHs causes pain and irritation at the site of injection. Applicants' invention is not directed to IGF-I per se, rather it is directed to compositions that allow for increased solubility of this protein at higher pHs and at refrigerated temperatures that promote stability of this protein. These compositions provide a means of administering comparable doses of IGF-I within a smaller volume and at a higher, less irritating pHs. In so doing, Applicants' invention has addressed a need in the art and should not be limited to IGF-I alone.

Secondly, the present specification clearly enables the pending claims. To be enabling under 35 U.S.C. §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. Furthermore, the test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect

to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *Johns Hopkins University v. Cellpro, Inc.*, 152F.3d 1342, 1360 (Fed. Cir. 1998).

Amended claims 1-20 recite biologically active IGF-I or a biologically active IGF-I analogue where the analogue is a compound selected from the group consisting of a compound that retains IGF-I activity, a compound that binds an IGF-I receptor, and a compound that retains IGF-I activity and binds an IGF-I receptor. IGF-I analogues are defined at page 5, lines 27-28. The specification provides several routine bioassays for testing activity of IGF-I analogues at page 5, line 29 through line 5, page 6. Amended claims 2, 15, and 20 recite arginine analogues where the analogue is an amino acid analogue that increases solubility of IGF-I at a pH of about 5.5 or greater. See page 7, lines 21-25, of the specification. Further guidance as to IGF-I analogue candidates is provided at page 5, lines 29-30, at page 6, line 7, through line 18 of page 7.

Given this disclosure, one of skill in the art could readily make analogues of IGF-I, test for their biological activity, use the methods of the invention, and readily determine, without undue experimentation, whether the composition comprising an IGF-I analogue and a solubilizing agent, as defined in the disclosure, constitutes the claimed IGF-I composition. It is clearly stated that the composition, at a temperature of about 4°C and a pH of at least about 5.5, will have IGF-I or its analogue "at a concentration of about 12 mg/ml or higher" and that the IGF-I analogue "will retain IGF-I activity and/or the ability to bind IGF-I receptors". See page 5, lines 27-28, and page 10, lines 20-26. As noted above, methods for determining IGF-I activity are well known in the art, and specific examples are disclosed in the specification at page 5, line 34, through line 6 of page 6. Likewise, for IGF-I or any one of its possible analogues, one of skill in the art could readily determine whether an amino acid analogue of arginine would retain the activity of enhancing solubility of IGF-I at a pH of about 5.5 or greater and at a temperature of about 4°C such that the claimed IGF-I composition has an IGF-I concentration of at least about 12 mg/ml under these pH and temperature conditions. Applicants' submit that the specification

does sufficiently teach one of skill in the art how to make and use the claimed invention. Thus, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

Claims 1-20 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants' regard as the invention. It is stated that the term "analogue" renders the claims indefinite. Applicants' respectfully traverse this rejection.

Amended claims 1-20 more clearly recite IGF-I analogues and arginine analogues as defined in the specification. The specification clearly teaches what is intended by "analogues" of IGF-I and arginine. See page 5, lines 27-34 through line 18 of page 7, more particularly page 7, lines 7-18, where IGF-I analogues known in the art are provided, and page 7, lines 21-25, where arginine analogues are defined as amino acid analogues of arginine that retain the activity of arginine with regard to the invention, i.e., that increase solubility of IGF-I at pH 5.5 or greater. One of skill in the art would be able to recognize whether a chemical substance was an analogue of IGF-I or arginine. Given the clear definition and description of analogues in the specification and amended claims, Applicants respectfully submit that the claims are definite and that the rejections under 35 U.S.C. §112, second paragraph, should be withdrawn.

The Rejections Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Clark *et al.*, U.S. Patent No. 5,126,324, and *The Merck Index* as applied to claims 1-20 and further in view of Chang *et al.*, U.S. Patent No. 5,410,026. This rejection is respectfully traversed.

The Clark *et al.* patent teaches a pharmaceutical composition comprising IGF-I, a growth hormone, and a solubilizing compound, such as a poloxamer, which is added to solubilize the growth hormone. Examiner asserts that this solubilizer should act in the same manner for IGF-I, as it is considered a pharmaceutic aid according to *The Merck Index*. However, there is no evidence in the Clark *et al.* reference, and no facts or evidence are presented by Examiner, that this assertion is true. Thus Examiner's "factual" assertion as presented is purely speculative and without foundation. Applicants cannot accept an assertion of fact without evidence and request

under 37 C.F.R. §1.104(d)(2) that the Examiner provide evidence that this solubilizing compound acts in the same manner for IGF-I as it does for growth hormone.

Furthermore, the solubilizing compounds used in the Clark *et al.* reference do not contain a guanidinium group. Thus a wholly different class of compounds is being used to solubilize IGF-I in the present invention. There is no suggestion in the Clark *et al.* reference that this different class of compounds would solubilize IGF-I in the manner encompassed in the present invention.

The Chang *et al.* patent is directed to a method for recovering correctly folded IGF-I from improperly folded, insoluble, non-biologically active IGF-I produced in a prokaryotic host. This secondary reference teaches the use of a chaotropic agent to render "the IGF-I up to about 90% soluble in the aqueous medium." Guanidine hydrochloride is disclosed as one such chaotropic agent. However, the chaotropic agent disclosed in this patent denatures the IGF-I protein, and hence the protein is not biologically active. The compositions of the present invention comprise biologically active IGF-I. The use of guanidine hydrochloride in the method of the present invention does not render the IGF-I protein inactive. Amended claims 1-20 recite a composition having biologically active IGF-I, as is stated in the specification at page 5, lines 19-20 and 27.

In view of these remarks, Applicants submit that the claimed invention is not taught by the cited references. Accordingly, the rejection of the claims under 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §112, first and second paragraphs, and 35 U.S.C. §103(a) are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper.

However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, DC 20231, on July 9, 1999.

Leslie T. Henry

RTA01/2064153v1